FOOD AND DRUGS AUTHORITY

GUIDELINES FOR REPORTING VARIATIONS TO A REGISTERED BIOLOGICAL PRODUCT IN GHANA

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FOREWORD

The Ghana Public Health Act 851 of 2012 requires that biological products, including vaccines intended to be marketed in Ghana meet the acceptable standards of quality, safety and efficacy and at the same time be assessed to have been produced in facilities that comply with current Good Manufacturing Practices (cGMP).

In the life cycle of a product, changes to the product that may impact on product quality, safety or efficacy should be communicated to the Food and Drugs Authority as variations to the product licence.

All post registration changes/variations that cannot be classified as minor, are classified as major variations by default.

This document is intended to provide guidance to applicants for the preparation and submission of variations to registered biological products in Ghana.

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Introduction

The specifications of biological products are defined for the issuance of the FDA product licence, which is valid for three years. To accommodate production, safety, and efficacy parameters which evolve with time, the product licence must be updated to reflect the product as it currently exists. Manufacturers are responsible for assessing the impact of planned and proposed changes on their product, and regulatory approval of the changes is needed to maintain the validity of the product licence. However, it is recognized that not all changes affect the product to the same extent. Some, like a change in the active ingredient, are so significant that the altered product is considered to be a new product, requiring a complete re-assessment and licensing procedure. Others, like the replacement of one equipment by another of similar technical characteristics and functioning principles, are considered as occurrences and are unlikely to affect product's quality.

In correspondence with good practices, usually the updating of a manufacturing process is well planned in advance, in such a way that allows an early evaluation of the improvement feasibility and potential impact in the process and product.

After the licensing of a biological product, it may happen that manufacturers introduce or plan to introduce changes in the manufacture of the product. Changes may be introduced to improve the quality of the biological product, the efficiency of the manufacturing process, or they could be made for marketing reasons. In addition, there may be changes to the labelling system of a biological product because of a new schedule, improving the management of a potential risk for a product by adding warnings, limiting or expanding the target population, etc.

Due to the implications and impact that these changes may have on the quality, safety and efficacy of the biological products, as well as to avoid additional regulatory burden, this guideline serves as a general scheme to classify post registration variations. Changes are currently categorized in two groups according to their significance or impact on the attributes of the biological product.

These groups are as follows:

I Major changes (M) with a high potential to affect the quality, safety or efficacy of the biological product.
II Minor changes (N) with a low potential to affect quality, safety, or efficacy.
Using this scheme, each change is classified according to how it is to be reported, and the amount of supporting information the manufacturer must submit.

Scope

This guidance document is applicable to manufacturers intending to make any post licensure changes in the production, quality control, indications etc. to registered biological products including vaccines.

Objectives

- To assist manufacturers with the classification of changes made to biological products;
- To provide guidance on the data package required in supporting changes that may potentially impact on the quality, safety and efficacy attributes of the biological products including vaccines.

Definition of Terms

In these guidelines, unless the context otherwise states:

- **BIOLOGICAL PRODUCTS** products derived from living organisms (ranging from normal or genetically modified microorganisms to fluids, tissues and cells derived from various animal and human sources) or containing living organisms that are used to;
  - Treat or prevent diseases or manage injury
  - Diagnose medical condition
  - Alter the physiological processes
  - Test the susceptibility to diseases

Such items include;

- Products of genetically modified organisms (e.g. insulin etc.)
- Traditional vaccines (bacterial, viral, combination etc.)
- Immunotherapy products (e.g. cell based tumour vaccines, human cellular vaccines etc.)
- Peptides and Polypeptides (e.g. insulin, cytokine etc.)
- Monoclonal antibodies
- Other human cell based products (e.g. fibroblast, epithelial cells, chondrocytes)

- **AUTHORITY** Food and Drugs Authority

- **PRODUCTS** biological product

- **APPLICANT** the product owner or license holder. Representatives of license holders may not hold themselves as applicants unless they own the product.

- **VARIATION** a change in the manufacturing process, product specification, indication(s), dosage recommendation (s), drugs classification and / or patients group(s) for a previously registered biological product been marketed under the same name in Ghana. A variation also includes, but not limited to, a change in the product name, site of manufacture and / or source of ingredients.

- **VACCINES** a heterogeneous class of medicinal products containing immunogenic substances capable of inducing specific, active and protective host immunity against infectious disease.

- **TRADITIONAL VACCINES** in the context of the expedited review procedure means Diphtheria and Tetanus toxoids and (whole cell) Pertussis vaccine (DTP), Bacille Calmette-Guerin (BCG), Oral Poliovirus Vaccines (OPV), products containing Diphtheria and Tetanus toxoids (DT/Td/TT), Measles, Yellow fever, Hepatitis B, and/or *Haemophilus Influenzae* type b conjugated (Hib) vaccines.

- **COMBINED VACCINE** vaccine that consists of two or more antigens, combined by the manufacturer at the final formulation stage or mixed immediately before administration. Such vaccines are intended to protect against more than one disease, or against one disease caused by different strains or serotypes of the same organism.

- **CONJUGATED VACCINE** a vaccine produced by covalently binding an antigen to a carrier protein with the intention of improving the immunogenicity of the attached antigen. This technique is most often applied to bacterial polysaccharides for the prevention of invasive bacterial disease.

- **ADJUVANT** a substance which when given in combination with an antigen augments the immune response to that antigen.

- **MANUFACTURER** any person involved in any stage of the manufacturing process, including any person involved in packaging and labelling, sterilising and testing, up to and including release for supply.

- **MASTER SEED LOT (MSL)** a homogenous suspension of the original cells or organisms on which production is based and aliquot into individual containers for storage. For genetically modified products, the cells in the MSL are normally already transformed by the expression vector containing the desired gene. In some cases, the MSL for the expression vector and MSL for host cells may be different.

- **WORKING SEED LOT (WSL)** a homogenous suspension of cells or organisms derived from the MSL under defined conditions and aliquot into individual containers for storage. The WSL is used at a defined passage level for routine production. Containers of MSL and WSL, once removed from storage, must not be returned to the seed lot stock.

- **BATCH (FINAL LOT)** collection of closed, final containers or other final dosage units that are expected to be homogenous and equivalent with respect to risk of contamination during filling or preparation of the final product. Preparation is from the same final bulk lot of the biological product, freeze-dried together (if applicable) and closed in one continuous working session.

- **STABILITY OF VACCINES** the ability of a vaccine to retain its chemical, physical, microbiological and biological properties within specified limits throughout its shelf-life.

- **STABILITY TESTS** a series of tests designed to obtain information on the stability of a vaccine in order to define its shelf-life and utilization period under specified packaging and storage conditions.

- **ACCELERATED STABILITY STUDIES** studies designed to determine the rate of change of vaccine properties over time as a consequence of the exposure to temperatures higher than those recommended for storage. These studies may provide useful support data for establishing the shelf-life or release specifications but should not be used to forecast real time real condition stability of a vaccine. They could also provide preliminary information on the vaccine stability at early developmental stages and assist in assessing stability profile of a vaccine after manufacturing changes.

- **STRESS TESTING** studies performed to determine the impact of extreme environmental factors such as light and extreme temperature. These studies are not usually performed as part of a stability program, but are used instead to establish protective packaging and container conditions, and to support exclusionary labelling.

- **SUPPORTING STABILITY DATA** supplementary data, such as stability data on small-scale batches, related formulations, and products presented in containers other than those proposed for marketing, and scientific rationales that support the analytical procedures, the proposed re-test period or the shelf-life and storage conditions.

- **STORAGE PERIOD** time period during which an intermediate may be held under appropriate storage conditions.

- **SHELF-LIFE** the period of time during which a product, if stored correctly, is expected to comply with the specification as determined by stability studies on a number of batches of the product. The shelf-life is used to establish the expiry date of each batch. Shelf-life is used for the final product; storage period is used for the intermediates. “Shelf-life specifications” are those specifications that should be met throughout the shelf-life of the product (should not be confused with “release specification”).

- **EXPIRY DATE** the date given on the individual container (usually on the label) of a final biological product up to and including which, the product is expected to remain within specifications, if stored as recommended. It is established for each batch by adding the shelf-life period to the date of manufacturing or the starting date of the last potency test.

- **CLINICAL TRIAL OR STUDY** a scientific investigation to assess efficacy and/or safety of a product under field conditions in a subjects and using the product in accordance with the label.

- **RESIDUAL PATHOGENICITY** the potential of viruses or bacteria which have been attenuated for specific route of administration to retain different levels of pathogenicity.

- **OVERDOSE** 2 × the maximum concentration but may be as high as 10 × in the case of live biological. Refer to relevant pharmacopoeia monographs where applicable.

- **FINISHED PRODUCT** the formulated product, in its final dosage form and held in the final sealed container and packaging in a form that is intended to be released for supply.

Reporting categories and procedure for submissions

To better explain what is needed for the reporting of variations introduced in the production and control of biological products including vaccines, this guidance document lists a number of changes likely to occur over the lifespan of a biological product, the timing for reporting to FDA Ghana, and required supporting evidence to justify the change. The reporting of variations covers the following categories: Minor (N) and Major (M) Variations some of which may require the Authority's approval before implementation. Minor variations are the same as Notifications.

If the Authority considers that a change(s) has been inappropriately classified, the manufacturer will be notified accordingly.

The Authority will review minor variations within 30 days of receipt of the notification and will update its records accordingly. If the Authority has not sent the manufacturer a written communication on the notification within 30 days following the acknowledgement of receipt of a valid notification, the notification shall be deemed acceptable.

	Description of the change	Conditions to be fulfilled	Supporting data	Reporting category
1.	**Change in the name and/or address of the marketing authorization holder that was granted the license of the biological product**.	1	1,2	N

Conditions
1.The marketing authorization holder shall remain the same legal entity

Supporting data
1. Approval for change of name as per statutory requirements.
2. Notification of new name if the manufacturer is sold or merged with another company. Note that if address changes due to site change then PSF needs to be resubmitted with fresh quality; safety and efficacy data.

	Description of the Change	Conditions to be fulfilled	Supporting Data	Reporting Category
2.	**Company sale, purchase, merger.**	1	1, 2,3	N

Conditions
1. The marketing authorization holder shall remain the same legal entity.

Supporting data
1. Approval for sale/purchase as per statutory requirements.
2. Notification of new name if the manufacturer is sold or merged with another company.
3. Revised labeling.

3.	**Change in the (invented) name of the product.**	1	1,2	N

Conditions
1. The NRA has authorized a new name.

Supporting data
1. Copy of the NRA letter of acceptance of the new (invented) name.
2. Revised product information.

4.	**Changes to cell banks:**			
	a) Generation of a new Master Cell Bank (MCB) from the same expression construct with same or closely related cell line; or generation of a new MCB from a different expression construct with the same coding sequence and the same cell line; or adaptation of a MCB into a new fermentation medium.	None	1-3, 5-8	M
	b) Generation of a new MCB	1	1-3, 5-7	M
	c) Generation of a new Working Cell Bank (WCB).	1	2– 4,1-2	M

5.	**Changes to the seed lots:**			
	a) New Master Seed lot (MSL); or Working Seed Lot (WSL) extended beyond an approved passage level.	None	3-7,9	M
	b) Generation of a new (WSB).	2-4	3-7	M

Conditions

1. The new MCB is generated from a pre-approved Master or Working Cell Bank.
2. The new cell bank/seed lot is generated from a pre-approved MCB/MSL.
3. The new cell bank/seed lot is at the pre-approved passage level.
4. The new cell bank/seed lot is released according to a pre-approved protocol.

Supporting data

1. Qualification of the cell bank.
2. Information on the characterization and testing of the post-production cell bank for recombinant product /non-recombinant product.
3. Comparability of the approved and proposed product with respect to physico-chemical characterization, biological activity, and impurity profile (notice that occasionally, the manufacturer may be required to undertake bridging non-clinical or clinical studies, to support the quality data).
4. Description of the batches and summary of results as quantitative data, in a comparative tabular format, for the new seed lot (certificate of analysis to be provided).
5. Description of the batches and summary of results as quantitative data, in a comparative tabular format, for at least three (3) consecutive commercial scale batches of the bulk derived from the new cell/seed lot (certificates of analysis to be provided).
6. Stability test results from a minimum of three (3) months of accelerated and three (3) months of real time/real temperature testing on three (3) commercial scale batches of the proposed bulk or longer if less than three (3) time points are available (including the zero time point), as well as commitment to notify FDA of any failures in the ongoing long term stability studies.
7. Updated, Quality Control (QC) approved post-approval stability protocol (or where applicable, the final version of the protocol to be signed by QC) and commitment to place the first commercial scale batch of the final product manufactured using the proposed bulk into the long term stability programme (quoting the corresponding procedure or SOP).
8. Supporting non-clinical and clinical data or a request for a waiver of *in-vivo* studies.
9. Supporting clinical data.

6.	**Changes to a bulk manufacturing facility, involving:**			
	a) Replacement or addition of a manufacturing facility for the bulk, or any intermediate of the bulk.	1-5,	1-7, 9-13,15	M
	c) Introduction of microbial hosts in to a multi–product mammalian cell culture suite or vice versa.	None	13 -14	M
	d) Conversion of production and related area (s) from campaign to concurrent for a multi - product facility.	6	16 -17	M
	e) Conversion of a bulk manufacturing facility from single-product to multi-product.	5	12 -13,15	M
	f) Addition of product (s) to an approved multi-product manufacturing facility.	4-5, 7	13,16	M
	g) Introduction of a different host/media-type into an approved multi-product facility.	7	8,15	M

	h) Deletion of a manufacturing facility or manufacturer for a bulk intermediate, or bulk.	None	None	M

Conditions

1. This is an addition of a manufacturing facility/suite to an approved manufacturing site.
2. The process is an exact replicate of the approved process and controls.
3. The new facility/suite is under the same Quality Assurance (QA)/Quality Control (QC) oversight.
4. No changes have been made to the approved and validated cleaning and change-over procedures.
5. The proposed change does not involve additional containment requirements.
6. The manufacturing process is a closed process for shared areas.
7. No changes to the cleaning protocol are necessary to support the introduction of new products (no changes in acceptance criteria, and no new materials have been introduced that need to be evaluated for clearance in a cleaning step).

Supporting data

1. Confirmation that the proposed manufacturing site has been inspected and is licensed by FDA and/or has been audited by WHO.
2. Updated Chapter 3or new dossier (CTD).
3. Name, address, and responsibility of the proposed production facility or facility involved in manufacturing and testing.
4. For antigenic substances obtained from, or manufactured with reagents obtained from sources that are at risk of transmitting Bovine Spongiform Encephalopathy (BSE)/Transmissible Spongiform Encephalopathies (TSEs) agents (e.g., ruminant origin), information and evidence that the material does not pose a potential BSE/TSE risk (e.g., name of manufacturer, species and tissues from which the material is a derivative, country of origin of the source animals, its use and previous acceptance). ATSE Certificate of Suitability from a qualified laboratory, if available, is acceptable for raw materials, auxiliary materials, and reagents only. This is also applicable for substances used in conjugation or linkages processes.
5. Information on the controls performed at critical steps of the manufacturing process and on the intermediate of the proposed bulk.
6. Summary of the process validation and/or evaluation studies. Reference to the protocols and validation reports. The complete report with all raw data could be requested during review and/or during a site audit.
7. Comparability of the approved and proposed bulk with respect to physico-chemical characterization, biological activity, and impurity profile (notice that occasionally, the manufacturer may be required to undertake bridging non-clinical or clinical studies, to support the quality data).
8. Information on the in-process control testing to demonstrate lack of carry-over or cross-contamination.
9. Description of the batches and summary of results as quantitative data, in a comparative tabular format, for at least three (3) consecutive commercial scale batches of the approved and proposed bulk (certificates of analysis to be provided).
10. Stability test results from a minimum of three (3) months of accelerated and three (3) months of real time/ real temperature testing on three (3) commercial scale batches of the proposed bulk, or longer if less than three (3) time points are available (including the zero time point), as well as commitment to notify FDA of any failures in the on-going long term stability studies. Manufacturer should consider quoting the corresponding procedures or SOPs for on-going studies.
11. Updated, QC approved post-approval stability protocol (or where applicable, the final version of the protocol to be signed by QC after NRA) and commitment to place the first commercial scale batch of the final product manufactured using the proposed bulk into the stability programme. Manufacturer should consider quoting the corresponding procedures or SOPs for on-going studies.
12. Information on the proposed production facility involved in the manufacture of the bulk, including the complete set of floor plans and flowcharts (drawings, room classification, water systems, HVAC systems), as well as the cleaning and shipping validation, as appropriate.
13. Information describing the change-over procedures for shared product-contact equipment and the segregation procedures, as applicable. If this is not the case, a signed attestation from the manufacturer that no changes were made to the change-over procedures.
14. Results of the environmental monitoring studies in critical classified areas.
15. Cleaning procedures (including data in a summary validation report and the cleaning protocol for the

introduction of new products, as applicable) demonstrating lack of carry-over or cross-contamination.
16. Data demonstrating lack of carry-over or cross-contamination.
17. Description of the segregation procedures to avoid cross-contamination. Manufacturer should consider quoting the procedures or SOPs in place.

7.	**Modification to a facility involved in the manufacture of a bulk, such as:**			
	a) For an intermediate of bulk manufactured in an open system, any changes which have the potential to increase the environmental risk to the product.	None	1-2, 5	M
	b) Relocation of equipment to another room in the same facility, qualification of a new room or change in classification of an existing room.	1-3	3-5	M
	c) Modification to a manufacturing area or to an existing service/system (e.g., change to WFI systems or HVAC systems, moving a wall).	1-2	3-5	M
	d) Change in the location of steps in the production process within the same facility.	1	4-5	M

Conditions
1. The change has no impact on the risk of contamination or cross-contamination.
2. The modification has no product impact.
3. Re-qualification of the equipment follows the original qualification protocol, if applicable.

Supporting data
1. Information on the in-process control testing.
2. Process validation and/or evaluation studies (e.g., equipment qualification). The proposed validation protocol is acceptable, but data could be requested.
3. Information demonstrating re-qualification of the equipment or re-qualification of the change (e.g., operational qualification, performance qualification), as appropriate.
4. Information on the modified production facility/area involved in manufacturing, including set of floor plans and flow charts (drawings, room classification, water systems, HVAC systems).
5. Results of the environmental monitoring studies in critical classified areas.

8.	**Change to the bulk fermentation process involving:**			
	a) Critical change (e.g., incorporation of disposable bioreactor technology).	None	1-3, 6-7, 9,11	M
	b) A change with moderate potential to adversely impact quality of the product (e.g., extension of the *in-vitro* cell age beyond validated parameters).	2, 4	2-3, 6,8, 10	M
	c) A non-critical change, such as: change in harvesting and/or pooling procedures which does not affect the method of manufacture, recovery, storage conditions, sensitivity of detection of adventitious agents, or production scale; or duplication of a fermentation train; or addition of identical or similar/comparable bioreactors.	1-6, 9-10	2-3, 6,8	M

9.	**Change to the bulk purification process involving**			
	a) A critical change (e.g., change that impact the viral clearance capacity of the process or the impurity profile of the bulk negatively).	None	1-2, 5-7,9, 11-12	M
	b) A change with moderate potential to adversely impact quality of the product (e.g., change in the chemical separation method, for example ion-exchange HPLC to reverse phase HPLC).	2, 4	1-2, 6,7, 10 - 11	M
		1-5	1-2, 6,8	M
10	**Scale-up of the manufacturing process**			
	a) At the fermentation stage.	11 -12	3, 6-7,9,11,14	M
	b) At the purification stage.	1, 3,5, 7	6-7, 9,11	M
11	**Change in supplier of auxiliary materials/reagents of biological origin (e.g., foetal calf serum, insulin, human serum albumin)**	None	4, 8,12-13	M
		8	4,8	M
12	**Change in source of auxiliary materials/ reagents of biological origin**	None	4, 7,12 -13	M
		8	4,7	M
13	**Introduction of reprocessing steps**	None	5, 8,10-11	M

Conditions

1. No change in the principle of the sterilization procedures of the bulk.
2. The change does not impact the viral clearance data or the chemical nature of an in activating agent for a vaccine.
3. No change in the specifications of the bulk outside of the approved ranges.
4. No change in the impurity profile of the bulk outside of the approved limits.
5. The change is not needed by recurring events arising during manufacture or because of stability concerns.
6. The change does not affect the purification process.
7. The scale-up is linear.
8. The change is for a compendia auxiliary materials/reagents of biological origin (excluding human plasma-derived materials).
9. The new fermentation strain is identical to the approved fermentation strain(s), if applicable.
10. No change in the approved *in-vitro* cell age.
11. No change in the proportionality of the raw materials (i.e. the scale-up is linear).
12. The scale-up involves the use of the same bioreactor (i.e. does not involve the use of a larger bioreactor).

Supporting data

1. Flow diagram (including process and in-process controls) of the proposed manufacturing process (es) and a brief narrative description of the proposed manufacturing process (es).
2. Information on the quality and controls of the materials (e.g., raw materials, starting materials, solvents, reagents, catalysts) used in the manufacture of the proposed bulk.
3. If the change results in an increase in the number of population doublings, information on the characterization and testing of the post-production cell bank for recombinant product, or of the bulk for non- recombinant product.
4. For bulks obtained from, or manufactured with reagents obtained from sources that are at risk of transmitting BSE/TSE agents (e.g., ruminant origin), information and evidence that the material does not pose a potential BSE/TSE risk (e.g., name of manufacturer, species and tissues from which the material is a derivative, country of origin of the source animals, its use and previous acceptance). ATSE Certificate of Suitability, if available, is acceptable for raw materials, auxiliary materials, and reagents only.
5. Process validation and/or evaluation studies (e.g., for aseptic processing and sterilization).
6. Comparability of the approved and proposed product with respect to physico-chemical characterization, biological activity, and impurity profile.
7. Description of the batches and summary of results as quantitative data, in a comparative tabular format, for at least three (3) consecutive commercial scale batches of the approved and proposed bulk (certificates of analysis to be provided).
8. Description of the batches and summary of results as quantitative data, in a comparative tabular format, for one (1) commercial scale batch of the approved and proposed bulk (certificate of analysis can be provided).
9. Stability test results from a minimum of three (3) months of accelerated and three (3) months of real time/ real temperature testing on three (3) commercial scale batches of the proposed bulk, or longer if less than three (3) time points are available (including the zero time point), as well as commitment to notify the FDA of any failures in the ongoing long term stability studies.
10. Stability test results from a minimum of three (3) months of accelerated and three (3) months of real time/real temperature testing on one (1) commercial scale batch of the proposed bulk, or longer if less than three (3) time points are available (including the zero time point), as well as commitment to notify FDA of any failures in the ongoing long term stability studies.
11. Updated, QC approved post-approval stability protocol (or where applicable, the final version of the Protocol to be signed by QC) and stability commitment to place the first commercial scale batch of the final product manufactured using the proposed bulk into the stability programme.
12. Information assessing the risk with respect to potential contamination with adventitious agents (e.g., impact on the viral clearance studies, BSE/TSE risk), orates Certificate of Suitability, if available.
13. Information demonstrating comparability of the auxiliary materials/reagents of both sources.
14. Rationale for regarding the bioreactors as similar/comparable, if applicable.

14	**Change in product-contact equipment used in the bulk manufacturing process, such as:**			
	a) Equipment having different operating principles/properties from those originally approved.	1-3	1-3	M
	b) Introduction of new product-contact equipment used in a critical step (e.g., change in equipment model for a continuous centrifuge, water bath for viral in activation).	1-3	1-3	M
	c) Replacement of equipment with an equivalent.	None	3	M

Conditions

1. The change does not affect equipment used in the fermentation process.
2. The manufacturing process is not impacted by the change in product-contact equipment.
3. The change has no product impact on the product

	Supporting data 1. Information on the in-process control testing. 2. Process validation and/or evaluation studies, including equipment qualification, as appropriate. The proposed validation protocol is acceptable, but data could be requested. 3. Information demonstrating re-qualification of the equipment (e.g., operational qualification, performance qualification).			
15	**Change in specifications for the materials, involving:**	None	1-2	M
	a) Raw materials, starting materials.	1, 3-4	1, 3-6	M
	c) Solvents, reagents, catalysts.	2-4	1, 3-6	M
16	**Change in the in-process controls performed at critical steps used in the manufacture of the bulk.**	3-8	2-6	M

Conditions

1. The change in specifications for the materials is/should be within the approved ranges.
2. The grade of the materials is the same or is of higher quality.
3. No change in specifications of the bulk outside of the approved ranges.
4. No change in the impurity profile of the bulk outside of the approved limits.
5. The change is not necessitated by recurring events arising during manufacture or because of stability concerns.
6. The replaced analytical procedure maintains or tightens precision, accuracy, specificity and sensitivity.
7. No change in the principle of the sterilization procedures of the bulk.
8. No change in the in-process control limits outside of the approved ranges.

Supporting data

1. Information on the quality and controls of the materials (e.g., raw materials, starting materials, solvents, reagents, catalysts) used in the manufacture of the proposed bulk.
2. Information on the controls performed at critical steps of the manufacturing process and on intermediates of the proposed bulk.
3. Updated, QC approved copy of the proposed bulk specifications (or where applicable, the final version of the specifications to be signed by QC), if changed.
4. Copies or summaries of analytical procedures, if new analytical procedures are used.
5. Copies or summaries of validation reports, if new analytical procedures are used.
6. Description of the batches and summary of results as quantitative data, in a comparative tabular format, for one (1) commercial scale batch of the approved and proposed bulk.

17	**Major change to the following process validation protocols used during the manufacture of the bulk: protocol for the manufacture of cell bank/seed bank, protocol for the introduction of product into an approved multi product facility, protocol for the cleaning of equipment (e.g., change in the worst-case scenario during cleaning validation process.**	None	1-2	M

Conditions

None.

Supporting data

1. Proposed validation protocol. Proper identification of the protocols. Status of the approval. Process validation and/or evaluation studies could be requested by the FDA.
2. Rationale for the change in the validation protocol.

18	**Changes affecting the quality control (QC) testing of the bulk, involving:**			
	a) Transfer of the QC testing activities for a non pharmacopoeia assay (in-house) to a new company or to a different facility within the same company.	None	1-2	M
	b) Transfer of the QC testing activities for a Pharmacopoeia assay (in-house) to a new company not listed on the Establishment License of the manufacturer/ sponsor.	1	1-2	M

Conditions

1. The transferred QC test is not a potency assay or a bioassay.

Supporting data

1. Information demonstrating technology transfer qualification.
2. Evidence that the new company/facility is GMP compliant.

19	**Change in the specifications used to release the bulk, involving:**			
	a) Deletion of a test.	None	1,6	M
	b) Addition of a test.	1-2	1-3, 6	M
	c) Replacement of an analytical procedure.	None	1-3, 5-6	M
	d)Minor changes to an approved analytical procedure.	3-7	1, 5-6	M
	e) Change from an in-house analytical procedure to a pharmacopeia analytical procedure or change from an approved compendia. Analytical procedure to a harmonized compendia procedure.	3, 7	1-3	M
	f) Widening of an acceptance criterion.	None	1,6	M
	g) Tightening of an acceptance criterion.	8-9	1	M

Conditions

1. No change in the limits/acceptance criteria outside of approved ranges for approved assays.
2. The addition of a test is not to monitor new impurity species.
3. No change in the acceptance criteria outside of the approved ranges.
4. The method of analysis is the same and is based on the same analytical technique or principle (e.g., a change in column length or temperature, but not a different type of column or method) and no new impurities are detected.
5. Results of method validation demonstrate that the proposed analytical procedure is at least equivalent to the approved analytical procedure.
6. The modified analytical procedure maintains or tightens precision, accuracy, specificity and sensitivity.
7. The change does not concern potency testing.
8. The change is within the range of approved acceptance criteria.
9. Acceptance criterion for any Class 3 residual solvent is within the limits (e.g., as harmonized in ICH).

Supporting data

1. Updated, QC approved copy of the proposed bulk specifications (or where applicable, the final version of the specifications to be signed by QC).
2. Copies or summaries of analytical procedures, if new analytical procedures are used.
3. Copies or summaries of validation reports, if new analytical procedures are used. 4. Where an in-house analytical procedure is used and it is claimed to be identical to other standards, results of an equivalency study between the in-house/professed method/compendia methods should be performed.
5. Comparative results demonstrating that the approved and proposed analytical procedure are equivalent.
6. Justification of the proposed bulk specifications (e.g., test parameters, acceptance criteria, or analytical procedures).

20	**Reference Standards or Material:**			
	a) Change the reference standards from Pharmacopoeia to in- house.	None	1-2	M
	b) Change the reference standards from in- house/professed to pharmacopoeia.	1-2	1-2	M
	c) Qualification of a new lot of reference standard against the approved reference standard.	1-2	2	M
	d) Extension of reference standard shelf life.	2	3	M

Conditions

1. Qualification of the reference standard is performed according to the approved protocol (i.e.no deviation from the approved protocol; details of the protocol can be provided-dates, code, identification, status, level of approval).
2. The reference standard is not for a bacterial or a viral vaccine.

Supporting data

1. Revised Product monograph to reflect the change in reference standard.
2. Information demonstrating qualification of the proposed reference standards or materials (e.g., source, characterization, certificate of analysis).
3. Summary of stability testing and results to support the extension of reference standard shelf life.

21	**Container closure system(for bulk)**			
	a) Change in the primary container closure system (s) for the storage and shipment of the bulk.	None	1-2	M
		1-2	1,3	M

Conditions

1. The proposed container closure system is at least equivalent to the approved container closure system with respect to its relevant properties.
2. The change does not concern a sterile bulk.

Supporting data

1. Information on the proposed container closure system (e.g., description, specifications).
2. Demonstration of compatibility with the bulk.
3. Results demonstrating that the proposed container closure system is at least equivalent to the approved container closure system with respect to its relevant properties (e.g., results of transportation or interaction studies, extractable/leachable studies).
4. Stability test results from a minimum of three (3) months of accelerated and three (3) months of real time/ real temperature testing on three (3) commercial scale batches of the proposed bulk or longer if less than three (3) time points are available (including the zero time point), as well as commitment to notify the FDA of any failures in the ongoing long term stability studies. Results from one (1) batch may be sufficient based on

rationale.

22	**Change in the shelf life for the bulk or for a stored intermediate of the bulk, involving:**			
	a) Extension.	None	1-4, 6	M
		1-5	1-2, 5	M
	b) Reduction.	None	1-5	M
		6	2-4	M

Conditions

1. No changes to the container closure system in direct contact with the bulk with the potential of impact on the bulk; or to the recommended storage conditions of the bulk.
2. The approved shelf life is at least 24months.
3. Full long term stability data are available covering the proposed shelf life and are based on stability data generated on at least three (3) commercial scale batches.
4. Stability data were generated in accordance with the approved stability protocol.
5. Significant changes were not observed in the stability data.
6. The reduction in the shelf life is not necessitated by recurring events arising during manufacture or because of stability concerns (i.e.: problems arising during manufacturing or stability concerns should be reported for evaluation).

Supporting data

1. Summary of stability testing and results (e.g., studies conducted, protocols used, results obtained).
2. Proposed storage conditions and shelf life, as appropriate.
3. Updated, QC approved post-approval stability protocol (or where applicable, the final version of the protocol to be signed by QC) and stability commitment.
4. Justification of the change to the post-approval stability protocol or stability commitment.
5. Results of stability testing (i.e., full real time/real temperature stability data covering the proposed shelf life generated on at least three (3) commercial scale batches). For intermediates, data to show that the extension of shelf life has no negative impact on the production of the bulk.
6. Interim stability testing results and a commitment to notify FDA of any failures in the ongoing long term stability studies. Extrapolation of shelf life should be made in accordance with current regulations and must be justified.

23	**Change in the post-approval stability protocol of the bulk, involving:**			
	a) Major change to the post-approval stability protocol or stability commitment such as deletion of a test, replacement of an analytical procedure, change in storage temperature.	None	3-6	M
		1-2	1-2, 4-5	M
	b) Addition of time point (s) into the post-approval stability protocol.	None	4-5	M
	c) Addition of test(s) into the post-approval stability protocol.	3	4-5	M
	d) Deletion of time point (s) from the post approval stability protocol beyond the approved shelf life.	None	4-5	M
	e) Deletion of time point (s) from the post-approval stability protocol within the approved shelf life.	4	4-5	M

Conditions

1. For the replacement of an analytical procedure, the results of method validation demonstrate that the new analytical procedure is at least equivalent to the approved analytical procedure.
2. For the replacement of an analytical procedure, the new analytical procedure maintains or tightens precision,

accuracy, specificity and sensitivity.
3. The addition of test (s) is not due to stability concerns or to the identification of new impurities.
4. The approved bulk shelf life is at least 24 months.

Supporting data

1. Copies or summaries of analytical procedures, if new analytical procedures are used.
2. Copies or summaries of validation reports, if new analytical procedures are used.
3. Proposed storage conditions and or shelf life, as appropriate.
4. Updated, QC approved post-approval stability protocol (or where applicable, the final version of the protocol to be signed by QC) and stability commitment (according to established SOPs; reference to SOP should be done).
5. Justification of the change to the post-approval stability protocol or stability commitment.
6. If applicable, stability testing results to support the change to the post-approval stability protocol or stability commitment (e.g., data to show greater reliability of the alternate test).

23	**Change in the labeled storage conditions for the bulk, involving:**			
	a) Addition or change storage condition for the bulk (e.g., widening or tightening of a temperature criterion.	None	1–5	M
		1-2	1-4	M

Conditions

1. Change is not necessitated by recurring events arising during manufacture or because of stability concerns.
2. The change consists in the tightening of a temperature criterion within the approved ranges.

Supporting data

1. Revised product monograph(e.g., where applicable, title page, composition and packaging and Pharmaceutical information section) and inner and outer labels, as applicable.
2. Proposed storage conditions and shelf life.
3. Updated, QC approved post-approval stability protocol (or where applicable, the final version of the protocol to be signed by QC) and stability commitment.
4. Justification of the change in the labeled storage conditions/cautionary statement.
5. Results of stability testing (i.e.: full real time/real temperature stability data covering the proposed shelf life generated on one (1) commercial scale batch).

24	**Change in the controls (in-process tests and/or acceptance criteria) applied during the manufacturing process or on intermediates, such as:**			
	a) Deletion of an in-process test.	4-5	4	M
	b) Replacement or addition of an in-process test.	1, 4-6	1-3, 5	M
	c) Widening of an acceptance criterion.	None	1, 4-5	M
	d) Tightening of an acceptance criterion.	None	1, 4-5	M
		2	1	M

Conditions

1. The change is not necessitated by recurring events arising during manufacture or because of stability concerns.
2. The change is within the range of approved acceptance criteria.
3. Any new analytical procedure does not concern a novel, non-standard technique or a standard technique used in a novel way.
4. No change in the principle of the sterilization procedures of the finished product.
5. The deleted test has been demonstrated to be redundant with respect to the remaining tests.
6. Replaced or added analytical procedure maintains or tightens precision, accuracy, specificity and sensitivity.

Supporting data

1. Description of the proposed process controls or acceptance criteria.
2. Method validation for any new analytical procedures (reference to the protocols / validation reports, procedures used). The FDA, at any time, may ask for documented evidences.
3. Copies or summaries of analytical procedures, if new analytical procedures are used.
4. Data to show that the relaxation has not a negative impact on the quality of the batch. Results for at least one (1) commercial scale batch are required.
5. Rationale for the change supported by data.

25	**Major change to the following process validation protocols used during the manufacture of the final product: introduction of product into an approved multiproduct facility, protocol for the cleaning of equipment (e.g., change in the worst-case scenario during cleaning validation process)**	None	1-2	M

Conditions

None.

Supporting data

1. Proposed validation protocol (code, date of approval, plan, etc.). Process validation and/or evaluation studies could be requested. The FDA at any time may ask for documented evidences.
2. Rationale for the change in the validation protocol.

26	**Change in the description or composition of the final product, involving:**			
	a) Addition of a dosage form or change in the formulation (e.g., lyophilized powder to liquid, change in the amount of excipient, new diluents for lyophilized product).	None	1-10	M
	b) Change in fill volume (same concentration, different volume).	None	1-3, 5,7-9	M
		1, 3	2-4, 6,9	M
	c) Change in the concentration of the active ingredient (e.g., 20 unit/mL .vs. 10 unit/mL).	None	2-4, 6,8, 10	M
		2-3	2-4, 6,8	M
	d) Addition of a new presentation (e.g., addition of syringes to vials).	None	2-3, 6,8-10	M

Conditions

1. No major changes in the manufacturing process to accommodate the new fill volume.
2. The new concentration is bracketed by existing approved concentrations.
3. No change in the dose recommended.

Supporting data

1. Chapters of the dossier(CTD) should be updated accordingly
2. Confirmation that information on the bulk has not changed as a result of the submission (e.g., cross reference(s) should be provided to the previously approved dossier (CTD) or revised information on the bulk, if any of the attributes have changed.
3. Description and composition of the finished form.

4. Discussion of the components of the finished product, as appropriate (e.g., choice of excipients, compatibility of bulk and excipients, the leachates, compatibility with new container closure system (as appropriate)).
5. Batch formula, description of manufacturing process and process controls, controls of critical steps and intermediates, process validation and/or evaluation studies. Manufacturer may refer to these documents in the variation submission. FDA may request to review one or more of these documents if deemed necessary.
6. Control of excipients, if new excipients are proposed (e.g., specifications, confirmation that none of the excipients are prohibited).
7. Specification(s), analytical procedures (if new analytical methods are used), validation of analytical procedures (if new analytical methods are used), batch analyses (certificate of analysis for three (3) consecutive commercial scale batches. Bracketing for multiple strength products, container sizes and/or fills maybe acceptable if scientifically justified.
8. Information on the container closure system, if any of the components have changed (e.g., description, materials of construction, summary of specifications).
9. Stability test results from a minimum of three (3) months of accelerated and three (3) months of real time/ real temperature testing on three (3) commercial scale batches of the proposed final product, or longer if less than three (3) time points are available (including the zero time point), as well as commitment to notify the FDA of any failures in the ongoing long term stability studies.
10. Supporting clinical data or a request for a waiver of *in-vivo* studies.

27	**Change involving a chemical / synthetic adjuvant:**			
	a) Change in supplier/manufacturer of a chemical/synthetic adjuvant.	None	4-6, 10	M
		1-2	5	M
	b) Change in manufacture process of a chemical/synthetic adjuvant.	None	4-6, 10	M
		1-2	5	M
	c) Change in release specifications of a chemical/synthetic adjuvant (including the tests and/or the analytical procedures).	None	6-7, 10	M
		1, 3	7-9	M

Conditions
None.

Supporting data
1. Proposed validation protocol (code, date of approval, plan, etc.). Process validation and/or evaluation studies could be requested. The FDA at any time, may ask for documented evidences.
2. Rationale for the change in the validation protocol.

28	**Change involving a biological adjuvant:**			
	a) Change in supplier of a biological adjuvant.	None	1-7, 10 -11	M
	b) Change in manufacture of a biological adjuvant.	None	1-7, 10	M
		3	1-5, 7	M
	c) Change in release specifications of a biological adjuvant (the tests and/or the analytical procedures).	None	6-10	M
		1, 2	7-9	M

Conditions
1. No change in the release specifications of the adjuvant outside of the approved ranges.
2. Change in specifications consists in the addition of a new test or a minor change to an analytical procedure.
3. No change in the supplier of the adjuvant.

Supporting data.

1. Information assessing the risk with respect to potential contamination with adventitious agents (e.g., impact on the viral clearance studies, BSE/TSE risk).
2. Information on the quality and controls of the materials (e.g., raw materials, starting materials) used in the manufacture of the proposed adjuvant.
3. Information on the controls performed at critical steps of the manufacturing process and on intermediates of the proposed adjuvant.
4. Process validation and/or evaluation studies (e.g., for manufacturing of the adjuvant).
5. Description of the general properties, characteristic features and characterization data of the adjuvant.
6. Stability test results from a minimum of three (3) months of accelerated and three (3) months of real time/ real temperature testing on three (3) commercial scale batches of the proposed adjuvant, or longer if less than three (3) time points are available (including the zero time point), as well as commitment to notify FDA of any failure in the ongoing long term stability studies.
7. Updated, QC approval of the proposed specifications for the adjuvant (or final version of the specifications).
8. Copies or summaries of analytical procedures, if new analytical procedures are used.
9. Copies or summaries of validation reports, if new analytical procedures are used.
10. Description of the batches and summary of results as quantitative data, in a comparative tabular format, for at least three (3) consecutive commercial scale batches of the final product with the approved and proposed adjuvant, as applicable. Certificates of analysis to be provided.
11. Supporting non-clinical and clinical data, if applicable.

29	**Change to diluents, involving:**			
	a) Replacement of or addition to the source of a diluents.	None	1-7	M
		1-3	1	M
	b) Change in manufacture of a chemical/synthetic adjuvant.	None	4-6, 10	M
	c) Change in facility used to manufacture a diluent (same company).	1-2	3-4, 6-7	M
	d) Addition of a diluents filling line.	1-2, 4	1-4, 6	M

Conditions

1. The diluents are water for injection (WFI) or a salt solution.
2. After reconstitution, there is no change in the final product specifications outside of the approved ranges.
3. The proposed diluents is commercially available in the country of manufacture of the vaccine.
4. The addition of the diluents filling line in a filling facility approved by FDA

Supporting data

1. Flow diagram (including process and in-process controls) of the proposed manufacturing process (es) and a brief narrative description of the proposed manufacturing process (es).
2. Updated, QC approved copy of the proposed specifications for the diluents (or where applicable, the final version of the specifications to be signed by QC).
3. Description of the batches and summary of results as quantitative data, in a comparative tabular format, for at least three (3) consecutive commercial scale batches of the approved and proposed diluents (certificates of analysis to be provided as applicable).
4. Stability test results from a minimum of three (3) months of accelerated and three (3) months of real time/real temperature testing on three (3) commercial scale batches of the proposed diluent, or longer if less than three (3) time points are available (including the zero time point).
5. Updated stability data on the product reconstituted with the new diluent.
6. Cleaning procedures (including data in a summary validation report) demonstrating lack of carry-over or cross-contamination
7. Information on the proposed production facility involved in manufacturing of the diluent, including the complete set of floor plans and flow charts (drawings, room classification, water systems, HVAC systems).

30	**Change involving a final product manufacturer/manufacturing facility, such as:**			
	a) Replacement or addition of a manufacturing building for the final product (includes primary packaging facility).	None	1-8, 10 -13	M
		1-4	1-4, 6-8, 10	M
	c) Replacement of a formulation/filling suite or addition of an equivalent formulation/ filling suite.	1	3-4, 6-7, 9,11,13 –14	M
	c) Replacement or addition of a secondary packaging facility; a labeling/storage facility; or a distribution facility.	2-3	1-2, 4	M
	d) Deletion of a final product manufacturing facility.	None	None	M

Conditions

1. The formulation/filling facility is approved by FDA
2. No change in the composition, manufacturing process and final product specifications.
3. No change in the container/closure system.
4. The same validated manufacturing process is used.

Supporting data

1. Confirmation that the proposed manufacturing site is a GMP compliance facility.
2. Updated or new Drug Master File
3. Confirmation that information on the final product has not changed as a result of the submission (e.g., other Than change in facility) or revised information on the final product, if any of the attributes have changed.
4. Name, address, and responsibility of the proposed production facility involved in manufacturing and testing.
5. Description of the manufacturing process if different from the approved process and information on the controls performed at critical steps of the manufacturing process and on the intermediate of the proposed final product.
6. Process validation and /or evaluation studies (e.g., equipment qualification, media fills, as appropriate).
7. Description of the batches and summary of results as quantitative data, in a comparative tabular format, for at least three (3) consecutive commercial scale batches of the approved and proposed final product (certificates of analysis to be provided. Bracketing for multiple strength products, container sizes and/or fills may be acceptable if scientifically justified.
8. Summary of stability testing and results (e.g., studies conducted, protocols used, results obtained).
9. Commitment to place the first commercial scale batch of the finished product manufactured using the proposed formulation/filling suite into the stability programme, and to notify FDA of any failure in the ongoing long term stability studies.
10. Stability test results from a minimum of three (3) months of accelerated and three (3) months of real time/ real temperature testing on three (3) commercial scale batches of the finished product manufactured using the proposed manufacturing facility, or longer if less than three (3) time points are available (including the zero time point), as well as commitment to notify FDA of any failure in the ongoing long term stability studies. Bracketing and matrixing for multiple strength products, container sizes and/or fills may be acceptable if scientifically justified.
11. Information on the proposed production facility involved in the manufacture of the finished product, including the complete set of floor plans and flow charts (drawings, room classification, water systems, HVAC systems), as well as the cleaning and shipping validation, as appropriate.
12. Information describing the change-over procedures for shared product-contact equipment or the segregation procedures, as applicable. If no revisions, a signed attestation that no changes were made to the change–over procedures.
13. Results of the environmental monitoring studies in classified areas.
14. Rationale for considering the proposed formulation/filling suite as equivalent.

31	**Effect on the existing finished products in a finished product manufacturing facility involving introduction of a new product or change in concurrence:**			
	a) Conversion of a finished product manufacturing facility from single-product to	None	1-3	M

	multi-product).			
	b) Conversion of formulation and filling area(s) from campaign to concurrent for multiple product manufacturing areas.	1	1-2	M
	c) Introduction of new product into an approved multi-product formulation/filling suite.	2-4	1-3	M

Conditions

1. The manufacturing process is a closed process for shared areas.
2. The newly introduced product does not introduce significantly different risk issues.
3. The newly introduced product is not of significantly different strength (i.e., mg .vs .µg).
4. The maximum allowable carry-over is not affected by the introduction of the new product.

Supporting data

1. Cleaning procedures (including data in a summary validation report and the cleaning protocol for the Introduction of new products) demonstrating lack of carry-over or cross-contamination.
2. Information describing the change-over procedures for shared product-contact equipment or the segregation procedures, as appropriate. If no revisions, a signed attestation that no changes were made to the change-over procedures.
3. Information on the product (s) which shares the same equipment (e.g., therapeutic classification).

32	**Change in the final product manufacturing process, such as:**			
	a) Scale-up of the manufacturing process at the formulation/filling stage.	1-4	1, 3,5-6, 8, 10	M
	c) Addition or replacement of equipment (e.g., Formulation tank, filter housing, filling line and head, and lyophilizer).	None	1-4, 7,9	M
		5	3-4	M
	c) Product-contact equipment change from dedicated to shared (e.g., formulation tank, filter housing, filling line and head, lyophilizer).	None	9	M
	d) Addition of a new scale bracketed by the approved scales or scale-down of the manufacturing process.	1–4	1-3, 5,5, 10	M
	e) Change in process flow or procedures.	None	1-3, 5-6, 8	M

Conditions

1. The proposed scale uses similar/comparable equipment to that approved (N.B. change in equipment size is not considered as using similar/comparable equipment).
2. Any changes to the manufacturing process sand/or to the in-process controls are only those necessitated by the change in batch size (e.g., the same formulation, controls, standard operating procedures (SOPs) are utilized).
3. The change should not be a result of recurring events having arisen during manufacture or because of stability concerns.
4. No change in the principle of the sterilization procedures of the final product.
5. For product-contact equipment, the change is considered 'like for like' (i.e., in term of product-contact material/equipment size).

Supporting data

1. Description of the manufacturing process if different from the approved process and information on the controls performed at critical steps of the manufacturing process and on the intermediate of the proposed final product.
2. Information on the in-process control testing, as applicable.
3. Process validation and/or evaluation studies (e.g., equipment qualification, media fills, as appropriate).The

proposed validation protocol is acceptable, but data could be requested.

4. Information demonstrating qualification of the equipment (operational qualification, performance, qualification), or qualification of the change, as applicable.
5. Description of the batches and summary of result, in a comparative tabular format, for at least three (3) consecutive commercial scale batches of the approved and proposed product (certificates of analysis to be provided). Bracketing for multiple strength products, container sizes and/or fills may be acceptable if justified.
6. Summary of stability testing and results (e.g., studies conducted, protocols used, results obtained).
7. Commitment to place the first commercial scale batch of the final product manufactured using the proposed formulation/filling suite into the stability programme, and to notify the FDA of any failure in the ongoing stability studies.
8. Stability test results from a minimum of three (3) months of accelerated and three (3) months of realtime/ real temperature testing on three (3) commercial scale batches of the proposed product, or longer if less than three (3) time points are available (including the zero time point). Commitment to notify FDA of any failure in the ongoing long term stability studies. Bracketing and matrixing for multiple strength products, container sizes and/or fills may be acceptable if scientifically justified.
9. Cleaning procedures (summary validation report) demonstrating lack of carry-over or cross-contamination.
10. Rationale for regarding the equipment as similar/comparable, as applicable.

33	**Change in the standard/monograph (i.e. specifications) claimed for the excipient:**			
	a) Change in the standard/monograph (i.e. specification) claimed for the excipient.	None	1- 4	M
		1-5	1-4	M
	b) Change in the specification for an excipient to comply with an updated pharmacopoeia standard/monograph.	2-3	1, 2-4	M

Conditions

1. The change is from a house/professed standard to a pharmacopoeia standard/monograph.
2. The change is made exclusively to comply with a pharmacopoeia standard/monograph.
3. No change to the specifications for the functional properties of the excipient outside of neither the approved ranges nor that result in a potential impact on the performance of the finished product.
4. No deletion of tests or relaxation of acceptance criteria of the approved specifications, except to comply with a pharmacopoeia standard/monograph.
5. No deletion/change to analytical procedures, except to comply with a pharmacopoeia standard/ Monograph.

Supporting data

1. Updated excipient specifications.
2. Where a house analytical procedure is used and a standard/monograph is claimed, results of an equivalency Study between the house and compendia methods.
3. Justification of the proposed excipient specifications (e.g., demonstration of the suitability of the monograph to control the excipient and potential impact on the performance of the finished final product).
4. Declaration that consistency of quality and of the production process of the excipient is maintained.

34	**Change in the specifications used to release the excipient, involving:**			
	a) Deletion of a test.	5	1, 3-4	M
	b) Addition of a test.	4	1-4	M
	c) Replacement of an analytical procedure.	1-3	1-2	M
	c) Minor changes to an approved analytical procedure.	None	1-2	M
	d) A change from a house/professed analytical procedure to a Schedule	None	1-2	M

	analytical procedure.			
	f) To reflect a pharmacopoeia monograph update	None	1	M
	g)Widening of an acceptance criterion	4, 6	1, 3-4	M
	h)Tightening of an acceptance criterion	3-4	1	M

Conditions

1. Results of method validation demonstrate that the proposed analytical procedure is at least equivalent to the Approved analytical procedure.
2. The replaced analytical procedure maintains or tightens precision, accuracy, specificity and sensitivity.
3. The change is within the range of approved acceptance criteria or has been made to reflect new pharmacopoeia monograph specifications for the excipient.
4. Acceptance criterion for Class 3 residual solvent is within the accepted international limits (e.g., as per recognized by ICH).
5. The deleted test has been demonstrated to be redundant with respect to the remaining tests or is no longer a pharmacopoeia requirement.
6.The change to the specifications does not affect the functional properties of the excipient nor result in a potential impact on the performance of the final product.

Supporting data

1. Updated excipient specifications.
2. Where a house analytical procedure is used and a compendia standard is claimed, results of an equivalency study between the house and compendia methods.
3. Justification of the proposed excipient specifications (e.g., demonstration of the suitability of the monograph to control the excipient and potential impact on the performance of the finished product).
4. Declaration that consistency of quality and of the production process of the excipient is maintained.

35	**Change in the source of an excipient From a vegetable or synthetic source to a TSE risk (e.g., animal) source.**	None	2-8	M
36	**Change in the source of an excipient from a TSE risk (e.g., animal) source to a vegetable or synthetic source.**	2	1, 3,5-7	M
37	**Change in manufacture of a biological excipient.**	None	3-8	M
		2	3, 5-8	M
		1-2	3, 5	M
38	**Change in supplier for a human plasma-derived excipient (e.g., human serum albumin).**	None	4-9	M
		3-4	5-7, 10	M
39	**Change in supplier of an excipient of non-biological origin or of biological origin (exclude human plasma derived excipient).**	1	3	M

Conditions

1. No change in the specifications of the excipient or final product outside of the approved ranges.
2. The change does not concern a human plasma-derived excipient.
3. The excipient from the new supplier is a FDA approved excipient.
4. No chemistry and manufacturing changes were made by the supplier of the new excipient since its last approval by FDA.

Supporting data

1. Declaration from the manufacturer of the excipient that it is entirely of vegetable or synthetic origin.
2. Details of the source or the excipient (e.g., animal species, country of origin) and the steps under taken in processing to minimize the risk of TSE exposure.
3. Information demonstrating comparability in term of physico-chemical characterization and impurity profile of the proposed excipient with the approved excipient.
4. Information on the manufacturing process and on the controls performed at critical steps of the manufacturing process and on the intermediate of the proposed excipient.
5. Description of the batches and summary of results as quantitative data, in a comparative tabular format, for at least three (3) commercial scale batches of the proposed excipient (certificates of analysis to be provided).
6. Description of the batches and summary of results as quantitative data, in a comparative tabular format, for at least three (3) batches of the final product with the proposed excipient (certificates of analysis to be provided.
7. Stability test results from a minimum of three (3) months of accelerated and three (3) months of real time/ real temperature testing on three (3) batches of the final product with the proposed excipient, or longer if less than three (3) time points are available (including the zero time point), as well as commitment to notify FDA of any failures in the ongoing long term stability studies.
8. Information assessing the risk with respect to potential contamination with adventitious sagents (e.g., impact on the viral clearance studies, BSE/TSE risk).
9. Complete manufacturing and clinical safety data to support the use of the proposed human plasma derived excipient.
10. Letter from the supplier certifying that no changes were made to the excipient since its last approval by stringent regulatory authority.

40	**Change affecting the quality control (QC) testing of the finished product, involving:**			
	a) Transfer of the QC testing activities for a non pharmacopoeia assay (in-house) to a new company or to a different facility within the same company.	None	1-2	M

Conditions

1. The transferred QC test is not a potency assay or a bioassay.

Supporting data

1. Information demonstrating technology transfer qualification.
2. Evidence that the new company/facility is GMP compliant.

41	**Change in the specifications used to release the finished product, involving:**			
	a) For sterile products, replacing the sterility test with process parametric release.	None	1-2, 6,8-9	M
	b) Deletion of a test.	None	2, 8-9	M
	c) Addition of a test.	1-2	2-4, 8	M
	d) Change in animal species/strains for a test (e.g., new species/strains, animals of different age, new supplier where genotype of the animal cannot be confirmed).	None	5, 10	M
	e) Replacement of an analytical procedure.	None	2-4, 7	M
	f) Minor changes to an approved analytical procedure.	3-6	3-4, 7	M
	e) g)Widening of an acceptance criterion.	None	2, 8-9	M
	i) h) Tightening of an acceptance criterion.	7-8	2	M

Conditions

1. No change in the limits/acceptance criteria outside of the approved ranges for the approved assays.
2. The addition of test is not to monitor new impurity species.

3. No change in the acceptance criteria outside of the approved ranges.
4. The method of analysis is the same (e.g., a change in column length or temperature, but not a different type of column or method) and no new impurities are detected.
5. The modified analytical procedure maintains or tightens precision, accuracy, specificity and sensitivity.
6. The change does not concern potency testing.
7. The change is within the range of approved acceptance criteria.
8. Acceptance criterion for any residual solvent is within the international recommended specification (e.g., based on harmonized ICH limits).

Supporting data

1. Process validation and/or evaluation studies or validation protocol of the proposed finished product.
2. Updated, QC approved finished product specifications (final version to be signed by QC).
3. Copies or summaries of analytical procedures, if new analytical procedures are used.
4. Copies or summaries of validation reports, if new analytical procedures are used.
5. Data showing that change in animals gives comparable results with those obtained using approved animals.
6. Justification for the change to the analytical procedure (e.g., demonstration of the suitability of the analytical procedure to monitor the finished product, including the degradation products).
7. Justification of the proposed finished product specifications (e.g., demonstration of the suitability of the monograph to control the finished product, including degradation products).
8. Declaration that consistency of quality and of the production process is maintained.
9. Copies of relevant certificate of fitness for use (e.g., veterinary certificate)

42	**Change affecting the quality control (QC) testing of the finished product, involving:**			
	a) Change the reference standards from Pharmacopoeia to house.	None	1-2	M
	b) Change the reference standards from in-house / professed to pharmacopoeia.	1-2	1-2	M
	c) Qualification of a new lot of reference standard against the approved reference standard.	1-2	2	M
	d) Extension of reference standard shelf life.	2	3	M

Conditions

1. The transferred QC test is not a potency assay or a bioassay.
2. The reference standard is not for a bacterial or a viral vaccine.

Supporting data

1. Revised Product monograph to reflect the change in reference standard.
2. Information demonstrating qualification of the proposed reference standards or materials (e.g., source, characterization, certificate of analysis).
3. Summary of stability testing and results to support the extension of reference standard shelf life.

43	**Modification of a primary container Closure system, in contact with the medicinal product (e.g., new coating, adhesive, stopper, type of glass).**	None	1-7	M
		1-3	1, 3	M
44	**Change from approved single-dose container to multi-dose container.**	None	1-7	M
45	**Deletion of a container closure system.**	None	1	M

Conditions

1. No change in the type of container closure or materials of construction.
2. No change in the shape or dimensions of the container closure.
3. The change is made only to improve quality of the container and does not modify the product contact material (e.g., increase thickness of the glass vial without changing interior dimension).

Supporting data

1. Product monograph, dosage forms, composition, packaging, inner and outer labels, as appropriate.
2. Process validation and /or evaluation studies, or provide equivalency rationale.
3. Information on the proposed container closure system (e.g., description, materials, specifications).
4. Results demonstrating protection against leakage, no leaching of undesirable substance, compatibility with the product, and results from the toxicity and the biological reactivity tests.
5. Summary of stability testing and results (e.g., studies conducted, protocols used, results obtained).
6. Long-term stability studies; results of a minimum of three (3) months of accelerated and three (3) months of real time/real temperature testing on three (3) finished product batches, or longer if less than three (3) time points are available (including the zero time point), as well as commitment to notify FDA of any failures in the ongoing long term stability studies. Bracketing and matrixing may be acceptable if scientifically justified.
7. Information demonstrating suitability of the proposed container/closure system (e.g., last media fill's results, transportation and /or interaction studies demonstrating preservation of protein integrity and maintenance of the sterility, the sterility in multi-dose container).

46	**Change in the supplier for a primary container closure component, involving:**			
	a) Replacement or addition of a supplier.	None	1-2	M
		1-2	None	M
	b) Deletion of a supplier.	None	None	M

Conditions

1. No change in the type of container closure, materials of construction, shape, dimensions or in the sterilization process for a sterile container closure component.
2. No change in the specification of the container closure component outside of the approved ranges.

Supporting data

1. Data demonstrating the suitability of the container closure system (e.g., extractable/leachable testing).
2. Information on the proposed container closure system (e.g., description, materials of construction of primary packaging components, specifications).

47	**Change in the specifications used to release a primary or functional secondary container closure component, involving:**			
	a) Deletion of a supplier.	1-2	1-2	M
	b) Addition of a test.	3	1-2	M
	c) Replacement of an analytical procedure.	6-7	1-3	M
	c) Minor changes to an analytical procedure.	4-7	1-3	M
	e) Widening of an acceptance criterion..	None	1-2	M
	f) Tightening of an acceptance criterion.	8	1	M

Conditions

1. Deleted test has been demonstrated to be redundant or is no longer a pharmacopoeia requirement.
2. The change to the specifications does not affect the functional properties of the container closure component nor result in a potential impact on the performance of the final product.
3. The change is not necessitated by recurring events arising during manufacture or because of stability

concerns.
4. No change in the acceptance criteria outside of the approved ranges.
5. The new analytical procedure is of the same type.
6. Results of method validation demonstrate that the new or modified analytical procedure is at least equivalent to the approved analytical procedure.
7. New/modified analytical procedure maintains/tightens precision, accuracy, specificity and sensitivity.
8. The change is within the range of approved acceptance criteria or has been made to reflect new pharmacopoeia monograph specifications for the container closure component.

Supporting data

1. Updated, QC approved copy of the proposed specifications for the primary or functional secondary container Closure component (or where applicable, the final version of the specifications to be signed by)
2. Rationale for the change in specifications for a primary container closure component.
3. Description of the analytical procedure and, if applicable, validation data.

48	**Change in the shelf life for the final product, involving:**			
	a) An extension.	None	1– 4,6	M
		1-5	1-2, 5	M
	b) A reduction.	None	1-5	M
		6	2-4	M

Conditions

1. No changes to the container closure system in direct contact with the final product with the potential impact on the final product; or to the recommended storage conditions
2. The approved shelf life is at least 24 months.
3. Full long term stability data are available covering the proposed shelf life and are based on stability data generated on at least three (3) commercial scale batches.
4. Stability data were generated in accordance with the approved stability protocol.
5. Significant changes were not observed in the stability data.
6. The reduction in the shelf life is not necessitated by recurring events arising during manufacture or because of stability concerns (i.e. problems arising during manufacturing or stability concerns should be reported for evaluation).

Supporting data

1. Summary of stability testing and results (e.g., studies conducted, protocols used, results obtained).
2. Proposed storage conditions and shelf life, as appropriate.
3. Updated, QC approved post-approval stability protocol (or where applicable, the final version of the protocol to be signed by QC) and stability commitment.
4. Justification of the change to the post-approval stability protocol or stability commitment.
5. Results of stability testing (i.e., full real time/real temperature stability data covering the proposed shelf life generated on at least three (3) commercial scale batches).
6. Interim stability testing results and a commitment to notify FDA of any failures in the ongoing long term stability studies. Extrapolation of shelf life should be justified and based on valid and current regulatory documents.

49	**Change in the post-approval stability protocol of the final product, involving:**			
	a) Major change to the post-approval stability protocol or stability commitment such as deletion of a test, replacement of an analytical procedure, change in storage temperature.	None	3-6	M
		1-2	1-2, 4-5	M
	c) Addition of time point (s) into the post-approval stability protocol.	None	4-5	M
	d) Addition of test (s) into the post-approval stability protocol.	3	4-5	M

	e) Deletion of time point (s) from the post-approval stability protocol beyond the approved shelf life.	None	4-5	M
	f) Deletion of time point (s) from the post-approval stability protocol within the approved shelf life.	4	4-5	M

Conditions

1. For the replacement of an analytical procedure, the results of method validation must demonstrate that the new analytical procedure is at least equivalent to the approved analytical procedure.
2. For the replacement of an analytical procedure, the new analytical procedure maintains or tightens precision, accuracy, specificity and sensitivity.
3. The addition of test (s) is not due to stability concerns or to the identification of new impurities.
4. The approved final product shelf life is at least 24 months.

Supporting data

1. Copies or summaries of analytical procedures, if new analytical procedures are used.
2. Copies or summaries of validation reports, if new analytical procedures are used.
3. Proposed storage conditions and or shelf life, as appropriate.
4. Updated, QC approved post-approval stability protocol (or where applicable, the final version of the protocol to be signed by QC) and stability commitment.
5. Justification of the change to the post-approval stability protocol or stability commitment.
6. If applicable, stability testing results to support the change to the post-approval stability protocol or stability commitment (e.g., data to show greater reliability of the alternate test).

50	**Change in the labeled storage conditions for the final product or the diluted or reconstituted product, involving:**			
	a) Addition or change of storage condition for the final product (e.g., widening or tightening of a temperature criterion).	None	1-5	M
		1-2	1-4	M
	b) Addition of a cautionary statement.	1	1-2, 4-5	M
	c) Deletion of a cautionary statement.	None	1-2, 4,6	M

Conditions

1.The change is not necessitated by recurring events arising during manufacture or because of stability concerns.

2. The change consists in the tightening of a temperature criterion within the approved ranges.

Supporting data

1. Revised product monograph (e.g., title page, composition and packaging and pharmaceutical information and inner and outer labels, as applicable.
2. Proposed storage conditions and shelf life.
3. Updated, QC approved post-approval stability protocol (or where applicable, the final version of the protocol to be signed by QC) and stability commitment.
4. Justification of the change in the labeled storage conditions/cautionary statement.
5. Results of stability testing (e.g., full real time/real temperature stability data covering the proposed shelf life generated on one (1) commercial scale batch).
6. Results of stability testing (e.g., full real time/real temperature stability data covering the proposed shelf life generated on at least three (3) commercial scale batches).

Notes:

1. The following should be submitted to the Authority where applicable, with the relevant part of the dossier:
   (a) A cover letter.
   (b) A variation form
2. Minor variations pertaining to the administrative section to keep the product information up-to-date and to facilitate documentation management should be reported, as described in this document.
3. Any minor changes that have been implemented should be clearly identified in the affected documents (e.g., dossier (CTD, labels, package inserts, etc.) with the filing of any subsequent submission to the Authority.
4. For major variations, a 90 days evaluation timeline will apply.
5. The examples presented above are intended to assist manufacturers with the classification of changes made to products. The information summarized in the tables provides recommendations for:
   (a) The conditions to be fulfilled for a given change to be classified as either a minor variation or major variation change. If any of the conditions outlined for a minor change are not fulfilled, the change is automatically considered as a major variation.
   (b) The supporting data for a given change to be submitted to FDA by the applicant. Where applicable, the corresponding modules of the dossier for the

supporting data have been identified in brackets. An adequate rationale is required when supporting data cannot be provided; and

(c) The Authority reserves the right to request additional information, or conditions not specifically described in this document, as deemed appropriate.

6. For the purpose of this document **'test procedure'** has the same meaning as '**analytical procedure'** and **'limits'** have the same meaning as **'acceptance criteria'**. '**Specification parameter'** means the quality attribute for which a test procedure and limits are set, e.g. assay, identity and water content. The addition or deletion of a specification parameter therefore includes its corresponding test method and limits.

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